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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/704,159	08/28/96	WILLIAMS J	OPHD-02304

EXAMINER

18M1/0528

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ART UNIT	PAPER NUMBER
1816	5

DATE MAILED: 05/28/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire — 3 — month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-24 is/are pending in the application.
Of the above, claim(s) 1-9 and 15-24 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 10-14 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948. Substitute
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948 Substitute
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

Part III DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-9, drawn to a host cell, classified in Class 435, subclass 243.

Group II. Claims 10-14, drawn to a vaccine, classified in Class 424, subclass 184.1.

Group III. Claims 15-24, drawn to an antibody and a method of making an antibody, classified in Class 530, subclass 387.1.

2. The inventions of Groups I, II, and III represent separate and distinct products. They differ with respect to ingredients, method steps and final result. Host cells, vaccines, and antibodies therefore represent patentably distinct subject matter.

3. The inventions of Groups I/II and III are not related as products and a method of making or use. Therefore, they are patentably distinct.

4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Diane Ingolia on April 15, 1997, a provisional election was made without traverse to prosecute the invention of Group II, Claims 10-14. Claims 1-9 and 15-24 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Affirmation of this election must be made by applicant in responding to this Office action.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

7. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

8. Claims 1-24 are pending in this application. Claims 1-9 and 15-24 are withdrawn from further consideration. Claims 10-14 are being examined in this office action.

Claim Rejections - 35 USC § 112

9. Claims 10-12 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification does not enable a person of skill in the art to determine the exact amino acid residues to select for the claimed "portion" of the recited sequences.

Thus, the specification does not teach how to make functional polypeptide comprising portions of the particular sequences disclosed in the specification or a teaching of how to use them as *in vivo* vaccines commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the peptides disclosed in the specification or the breadth of peptides, recited in the claims. There is insufficient guidance to direct a person of skill in the art to know, for example, which portions when minimally sized portions are considered, if administered, would result in protection. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which sequences are required to retain similar activity and function requires a detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein are well outside the realm of routine experimentation. Therefore, it is unpredictable whether any of the "portions" to which the claims are drawn would be active in the instant protein. The true fact of the state of the art in peptide chemistry is expressed succinctly by Rudinger [Peptide Hormones, Parsons (Ed.), University Park Press, Baltimore, MD, Pp. 1-7]: "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (see the Conclusions in particular).

From the discussion above, it is clear that the predictability of changes to an amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the broad scope of the claims including any number of fragments or portions of any size. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an

area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the changes which can be made in the protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In view of the lack of predictability of the art to which the invention pertains and the limited working examples, the state of the prior art, the lack of guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the invention as broadly claimed and this is not sanctioned by the statute.

10. Claims 10-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 10-12 are indefinite for reciting "portion of" because the relevant portions have not been identified.

B. Claims 10-11 are indefinite for reciting "at least a portion of" because it is unclear how much of the *Clostridium* peptide is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson *et al.* [Eur. J. Biochem. 189: 73-81 (Apr 1990)] in view of Binz *et al.* [J. Biol. Chem. 265: 9153-9158 (June 1990)], Roitt [Essential Immunology, Sixth Edition, Blackwell Scientific Publications, Boston, MA, pp. 173-178 (1988)], LeClerc *et al.* [J. Immunol. 144 (8): 3174-3182 (Apr 1990)], Kleid [Annals NY Acad. Sci. 413: 23-30 (1983)], and Siegel [J. Clin. Microbiol. 26: 2351-2356 (Nov 1988)].

Thompson *et al.* teach the entire amino acid sequence of the *C. botulinum* type A neurotoxin (BoNT/A) deduced by nucleotide sequence analysis of the encoding gene (Figure 3, in particular). Thompson *et al.* teach that the light chain has the pharmacological activity (Page 73, Column 1, in particular). Thompson *et al.* teach that the increased use of neurotoxins in the food industry, in neurobiochemical research, and in clinical uses, requires immunization of personnel. Thompson *et al.*

teach that the availability of the BoNT/A gene sequence will allow the production of toxin and toxoid for the formulation of improved vaccines (Page 83, Last paragraph, in particular). Thompson *et al.* teach the association of receptor binding properties with the C-terminal portion of the heavy chain (Page 73, in particular).

Thompson *et al.* do not teach a vaccine comprising a fusion protein, said fusion protein comprising a non-toxin protein sequence and at least a portion of a *Clostridium botulinum* toxin, said toxin selected from the group consisting of type B toxin and type E toxin. However, Binz *et al.* teach the complete sequence of type A and a partial sequence of Type E. Roitt, in his textbook on immunology teaches that recombinant antigens can be generated such as viral epitopes and synthetic peptides. Use of fusion proteins in vaccine production is well known in the art. Two examples of the utilization of fusion proteins for generating vaccines are LeClerc *et al.* and Kleid. LeClerc *et al.* teach the expression of two viral epitopes (C3 neutralization epitopes from poliovirus type 1 and a viral epitope from hepatitis B) in E. coli periplasm as protein fusion with the maltose binding protein, the subsequent immunization of rabbits with the fusion protein, and the generation of antibodies of high titer against the viral peptide and corresponding virus. Kleid teaches using genetically engineered bacteria for vaccine production. Kleid teaches that biosynthetically produced Foot and Mouth Disease virus (FMDV) VP1-specific fusion proteins are effective vaccines.

Siegel teaches the pentavalent botulinum (ABCDE) toxoid vaccine manufactured by the Michigan Department of Public Health (MDPH) and that human response to MDPH vaccine was significantly greater than to a Parke, Davis, and Co. product in use for many years prior to the MDPH vaccine except for responses to types A and E (Page 2351, in particular). Siegel teaches analyses of the immune response of personnel immunized with the pentavalent vaccine. Sera from personnel were analyzed for neutralizing antibodies to type A and type B botulinum toxins after receiving a series

of immunizations and boosters. Neutralization titers improved after boosting (Tables 1, 2, and 3, in particular). Siegel teaches that an additional injection at 6 months into the immunization protocol is advantageous (Page 2355, Lines 10-15, in particular).

Therefore, a person of ordinary skill in the art would have been motivated at the time of the invention to immunize with fusion proteins comprising portions of type A toxin, type B toxin, and type E toxin polypeptide of type A, substituting the fusion peptides for a step in the immunization series or boosts with the pentavalent botulinum (ABCDE) toxoid vaccine in order to increase the response to type A and type E botulinum toxin because the response to toxins A and E needed improvement. A person of ordinary skill in the art would have had ample expectation of success of being able to utilize such methods because such methodology was well known in the art at the time the invention was made. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson *et al.* [Eur. J. Biochem. 189: 73-81 (Apr 1990)], Binz *et al.* [J. Biol. Chem. 265: 9153-9158 (June 1990)], Roitt [Essential Immunology, Sixth Edition, Blackwell Scientific Publications, Boston, MA, pp. 173-178 (1988)], LeClerc *et al.* [J. Immunol. 144 (8): 3174-3182 (Apr 1990)], Kleid [Annals NY Acad. Sci. 413: 23-30 (1983)], and Siegel [J. Clin. Microbiol. 26: 2351-2356 (Nov 1988)], as applied to claims 10-12 above, and further in view of Ford *et al.* [Protein Expression and Purification 2: 95-107 (1991)].

Thompson *et al.*, Binz *et al.*, Roitt, LeClerc *et al.*, Kleid, and Siegel do not teach a vaccine wherein the non-toxin protein sequence comprises a poly-histidine tract.

However, Ford *et al.* teach fusion tails comprising poly(his) residues for recovery by immobilized metal affinity chromatography (Page 100, in particular) or maltose-binding protein (MBP) of *E. coli.* as an N-terminal tail for purification (Page 98, in particular). Ford *et al.* teach that by genetically engineering the target protein to contain a specific affinity or interactive fusion tail, such biospecific tails can provide powerful tools for protein recovery and purification, allowing a specific target protein at a very low initial concentration to be purified in a single step from a complex mixture of proteins. Ford *et al.* teach that fusion tails have also been used to enhance the stability of small heterologous target proteins, preventing their proteolytic degradation, and to provide easily assayable "tags" to monitor the presence of a target protein during purification (Page 95, Paragraph 1, in particular).

Therefore, a person of ordinary skill in the art would have been motivated at the time of the invention to generate fusion proteins consisting of toxin A, toxin B or toxin E, or combinations of the individual toxins together with a non-toxin protein sequence such as poly(his) purification and recovery of the recombinant toxins. Following LeClerc's example of using fusion proteins for vaccination, one would have been motivated to substitute poly-histidine for the maltose binding protein of LeClerc *et al.* in order to facilitate purification of the fusion protein and thus ensure large quantities of pure immunogen. It would have been obvious for one to keep the vaccine endotoxin-free as that was the standard of the art for a pharmaceutical at the time the invention was made. A person of ordinary skill in the art would have had ample expectation of success of being able to utilize the above methods because such methodology was well known in the art at the time the invention was made. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Rabin, Ph.D. whose telephone number is (703) 305-6811. The examiner can normally be reached on Monday through Friday from 9:30 AM to 6:00 PM.

16. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The FAX number for this Group is (703) 305-7939. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Evelyn Rabin

Evelyn Rabin, Ph.D.
May 19, 1997

FRANK C. EISENSCHENK
PRIMARY EXAMINER
GROUP 1800
5/27/97